Exploring the multifocal role of phytochemicals as immunomodulators

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ABSTRACT

A well-functioning immune system of the host body plays pivotal role in the maintenance of ordinary physiological and immunological functions as well as internal environment. Balanced immunity enhances defense mechanism against infection, diseases and unwanted pathogens to avoid hypersensitivity reactions and immune related diseases. The ideal immune responses are the results of corrective interaction between the innate immune cells and acquired components of the immune system. Recently, the interest towards the immune system increased as significant target of toxicity due to exposure of chemicals, drugs and environmental pollutants. Numerous factors are involved in altering the immune responses of the host such as sex, age, stress, malnutrition, alcohol, genetic variability, life styles, environmental-pollutants and chemotherapy exposure. Immunomodulation is any modification of immune responses, often involved induction, amplification, attenuation or inhibition of immune responses. Several synthetic or traditional medicines are available in the market which promptly have many serious adverse effects and create pathogenic resistance. Phytochemicals are naturally occurring molecules, which significantly play an imperative role in modulating favorable immune responses. The present review emphasizes on the risk factors associated with alterations in immune responses, and immunomodulatory activity of phytochemicals specifically, glycosides, alkaloids, phenolic acids, flavonoids, saponins, tannins and sterols and sterolins.

1. Introduction

The immune system of the host plays a pivotal role in the maintenance of ordinary physiological and immunological functions as well as internal environment. Any disturbance in the functioning of immune system may lead to numerous lethal disorders for instance, rheumatoid arthritis, cancer and other inflammatory disorders [1]. The immune system is a complex network which mainly comprises of white blood cells (lymphocytes, monocytes, neutrophils and macrophages) and specific immune substances (antibodies, proteins and cytokines) that have been produced to provide the protection and resistance against various infections and diseases. The interaction between the numerous immune cells with these mediator's prompt to the formation of ideal immune responses [2]. The main characteristics of immune system is the distinction between its own cells or foreign pathogens [3]. Subsequently, it performs various interconnecting actions such as microbial detection, inflammation, microbial clearance, cell or tissue damage, death as well as heeling of wounds. The host immunity serves as a defense system which restricts the insertion of various pathogens and allows timely negotiation of immune cells with these substances into the tissue of microbes or pathogens to maintain the balance [4]. Redox homeostasis in the immune cells also provides the protection against various diseases. Consequently, the failure in the balance may leads to the development of immune mediated

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diseases such as metabolic syndrome, infections, dermatitis, inflammatory bowel disease and cancers. The ideal immune responses mainly have three core components which are recognition of the insertion of pathogens, phagocytosis reaction and sparing the issues of the individual [5]. The human body has immune responses which are classified as innate immunity and adaptive immunity which serves the specific responses against the pathogens and microorganisms (Fig. 1). The innate immunity, termed as non-specific immune system, is responsible for primary defense system which works against numerous pathogens whereas the adaptive immunity, termed as acquired or specific immune system, is produced gradually and serves as the defensive action against the infections [6]. The occurrence of memory cells facilitates these responses as they detect the invasion of similar antigen. The lack of these long-term memory cells in innate immunity provides incomplete protection against the foreign pathogens [7]. This innate immune system comprises of complement, phagocytic cells, acute phase proteins and specific types of receptors named toll-like receptors (TLRs). TLRs are the integral part of recognized receptor hierarchy, found in plants as well as in vertebrate and invertebrate animals, which have ability to detect the preserved molecular configuration associated with respective pathogen such as cell wall components (bacterial lipopeptides, β-glucans and lipopolysaccharides) of fungus and bacteria [8]. TLRs as well as other recognized receptors permit intrinsic cells to differentiate their own cells from foreign cells but in certain cases, they lack the ability to recognize between non self-molecules. For instance, the ability to respond against pathogenic and non-pathogenic bacteria is distinctive [9]. An assembly of blood proteins known as complement, which stimulates by the microbial surface molecules, damages the membrane of the microorganism, causing phagocytosis with the help of macrophages and neutrophils, and subsequently leading to the inflammatory responses. Foreign substances can also be killed by the group of antimicrobial peptides, degrading enzymes as well as by the reactive oxygen species (ROS). Furthermore, such combinations are utilized by phagocytic cells in order to produce signaling molecules which activate an inflammatory action as well as initiate in order to assemble strength of the adaptive immune system. The affected cells generate interferons (IF) that further induce number of cellular responses in order to cease the reproduction of virus within the cells as well as also promote cell destruction mode of cytotoxic T-lymphocytes and natural killer cells [10]. The acquired immune responses are powerful immune responses which comprise of long-term memory cells (T-cells, B-cells) and other specific receptors. All pathogens are identified by the signature antigen present in the cells [11]. The cell-mediated immune responses occur due to T-cells while humoral immune response take place due to B-cells. These cells attain specific receptors which recognize the main targets. T-cells (gamma-delta T-cells, helper T-cells, killer T-cells) recognize the invading pathogens only after the antigen processing while B-cells have B-cell antigen specific receptors on their surface which recognize the entire pathogens without any requirement of antigen processing. Moreover, these cells have ability to remember particular antigen and serve as protection against various pathogens to the host [12,13].

Both innate and adaptive immune system are working together in coordination optimistically. The innate immunity identifies pathogens as well as alerts adaptive immune system by the antigen configuration. The innate cells also produce chemokines and cytokines for the complete activation of adaptive immunity. Additionally, T-cells and B-cells are responsible to manage and terminate the immune responses after killing antigen, finally, circumventing unnecessary immune responses [13,14]. Despite the high specificity as well as efficacy and imbalance of immune responses may results in occurrence of numerous diseases like autoimmune disease, allergy, AIDS, hypersensitivity and immunosuppressive diseases [15,16]. Presently, the incidence of immunological diseases is rapidly increasing, as revealed by the epidemiological data, thus, leading to the evolution of immunomodulators. The immunomodulators are synthetic, biological or natural molecules which have the ability to modulate (increase or decrease) the immune responses of both innate as well as adaptive immune system in immune-related diseases. It has also been used to reestablish the imbalance of immune response. The interest in the

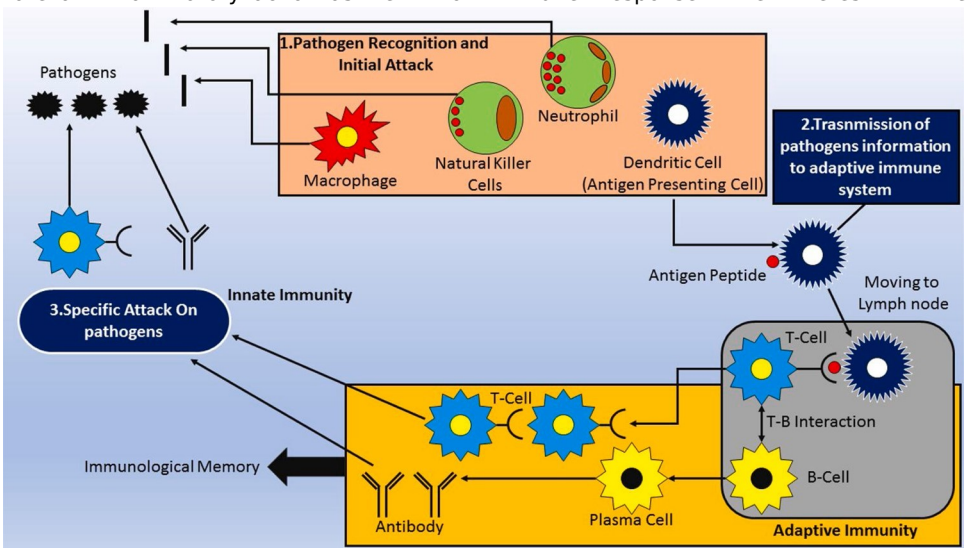


Fig. 1. Overview of immune system: Innate immunity and adaptive immunity.

development of new immunomodulators is promptly rising as the better understanding of the immune related diseases [17,18]. Clinically, immunomodulant are divided in three main categories: immunostimulant, immunosuppressant and immunoadjuvant. Immunostimulants are those molecules which have potential to stimulate immune responses in immunodeficiency diseases while immunosuppressive are those agents which are used to block the immune response in numerous immune-medicated disease such as autoimmune disease and organ transplantation. Immunoadjuvant are those agents which are added to a vaccine to facilitate the immune response [19]. However, numerous synthetic immunomodulator agents have been developed and established with their specific mode of action but they clinically failed to deliver the favorable therapeutic action due to their bioavailability and stability problems as well as serious adverse effects [20]. Thus, a new approach is required for the development of novel immunomodulators to manage the immune related disease with lesser or no side effects.

Natural plants and their active metabolites play an imperial role in the management of immunological diseases by modulating immune responses. Recently, phytochemicals have gained a great interest due to their multi-pharmacological activities such as immunomodulatory and antioxidant activities [21].

Phytochemicals are naturally occurring molecules mainly found in fruits, vegetables as well as in various medicinal plants. However, such secondary metabolites are not remarkably significant in terms of nutrition but still these are beneficial for the development cycle of plants as they protect plants from insects, pathogens, microorganism etc [22,23]. Moreover, phytochemicals play an empirical role in many processes during the growth of plant and also exhibit various features such as color, fragrance, flavor and texture to plant [24]. Various beverages which are obtained from nuts, herbs, vegetables and plants comprise of phytochemical molecules. Currently, such molecules of phytochemicals can be manipulated by many researchers for the cure of certain chronic diseases like diabetes or cancers [25].

In this present review, author gives a comprehensive description about the immunomodulatory activities of phytochemicals in the management of numerous chronic/life-threatening diseases. The review collaborates PUBMED (1993–2020), google scholar (1993–2020) and research gate databases (1993–2020), which were explored using keywords and their combinations such as immunomodulators, polyphenols, alkaloids, glycosides, polysaccharides, lectins, saponins, phytosterols, tannins, flavonoids and phenolic acids and several others, to create an extensive manuscript. Author also includes abstracts from national and international meetings in the present manuscript that make it more informative.

2. Classification of immunomodulators

Clinically, immunomodulants are divided in three main categories: immunostimulant, immunosuppressant and immunoadjuvant (Fig. 2).

2.1. Immunostimulants

These molecules are used to facilitate the immune responses against various infections (autoimmunity, allergy, cancer) by promptly activating both innate as well as adaptive immune system. Supposedly, these agents exhibit prophylactic action in the healthy individuals by stimulating the primary immune response and act as an immunotherapeutic agent in patients having primary and secondary immunodeficiency [26–28]. These agents do not alter the memory cells of immune system and also have a short duration of pharmacological activity. Thus, to maintain or enhance the therapeutic activity, they are re-administered in some interval of time or continuously re-administered [29].

2.2. Immunosuppressants

These molecules are used to suppress the pathological immune responses in autoimmune diseases, hypersensitivity, graft-versus-host-rejection, graft rejection and other immune mediated diseases. Aforementioned disease, these agents are amply utilized in the cure of graft rejection and autoimmune disorders. Rejection process by the immune system is a leading cause of morbidity, thus, immunosuppressants have the potency to decrease the potential of human body which reject the transplanted organs for instance, kidney, liver and heart. Hence, these molecules can also be termed as antirejection agents [30,31].

2.3. Immunoadjuvant

These molecules are used to facilitate the immune system by increasing magnitude, duration and induction of antigen specific immune response while they do not contain any special antigenic activity. These molecules are mainly administered in combination with specific vaccine antigen. In the absence of vaccine, these substances do not exhibit any antigen activity. Adjuvants may perform various favorable functions. These molecules act as a depot for gradual liberation of antigen, stimulate phagocytosis and improve the immune response produced by the only antigen [32]. These substances also indicate the danger signals to the immune system to respond

against specific antigen which may cause infection in the body. Freund's adjuvant is one of the well-known examples of this class. These molecules are utilized to distinguish between the Th1 and Th2, cellular and humoral, immunoglobulin G and immunoglobulin E, and immunoprotective and immunodestructive type of immune actions. These efforts have become a real challenge for the vaccine designer [33–35].

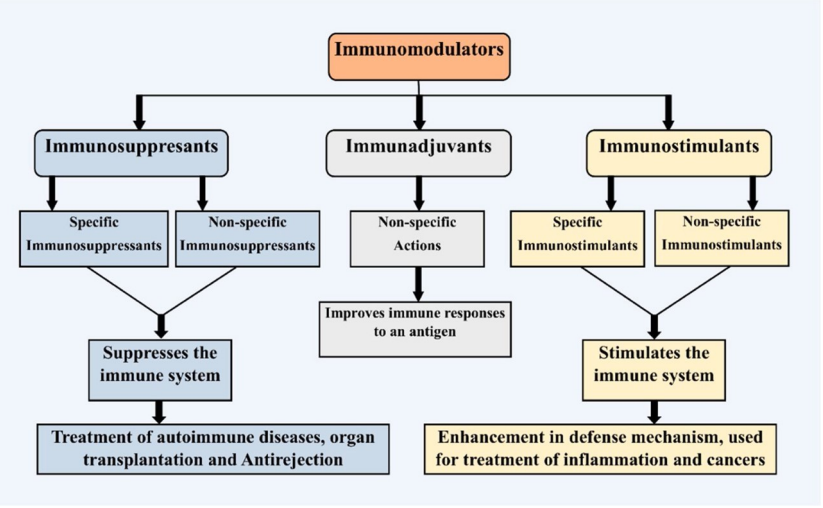


Fig. 2. Classification of immunomodulators and their mode of actions.

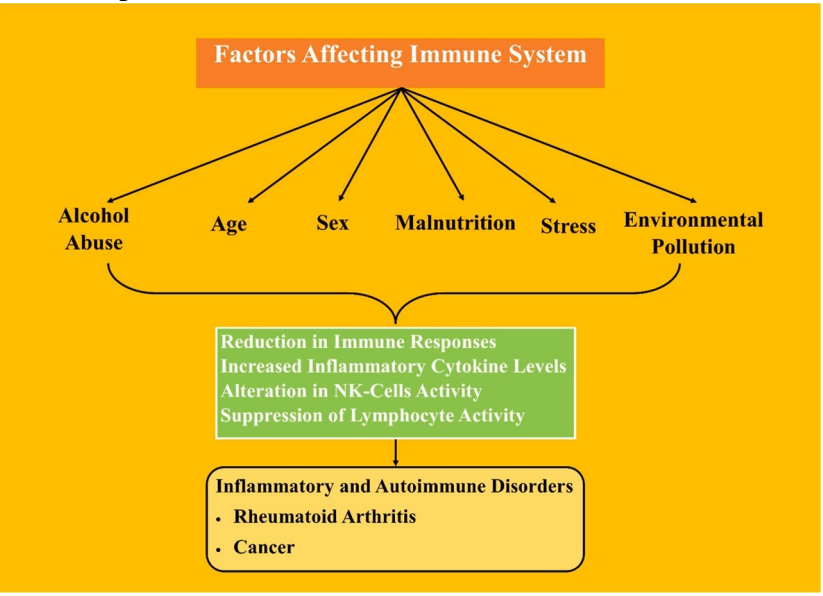


Fig. 3. Factors affecting immune system.

3. Factors associated with modification of immune system

There are various elements which play empirical role in alteration of immune system such as age, sex, environmental factor, stress, malnutrition and immunomodulation as shown in Fig. 3.

3.1. Age

Aging process reduces the functionality of immune system; thus, it contributes to enhance the prevalence various infection disease, autoimmune disease, cancer and also failure of vaccine therapy. Immunosenescence may lead to the alteration of numerous types of cells in thymus, bone marrow, lymphocytes in peripheral blood and other components of innate immunity. Typically, both the innate and adaptive immune system are affected by the aging process [36]. The innate immune system acts as the primary defense mechanism against pathogen invading. Aging process reduced this specific function of innate immunity which permits the entry of pathogens or microorganisms into the mucosal tissue of the host, consequently enhancing the challenge for the immune response. It is

observed that the levels of interleukins (IL)-1β, IL-6 and tumor necrosis factor alpha (TNF-α) increased in geriatrics which are main predictive biomarkers of the morality and fatality. The process of mutation of T-cells occurs in the thymus. Immunosenescence alters the morphology of the thymus which is characterized by depletion of organ size and substitution of functional cortex by fat. Subsequently, the existence of T-cells in thymus also declined by aging. It also affects the functionality of B-cells, resulting in alteration of adaptive immune system. However, the number of peripheral B-cells are not declined but it alters the composition of the compartments. Aging promptly affects the native B-cells thus, increases the susceptibility of occurrence of various infections and apoptosis in older people [36–38].

3.2. Sex

Sex dependent factors also play a crucial role in the progression and susceptibility towards various diseases. The prevalence and severity of various infectious diseases is observed more in men as compared to women due to sex steroid. The presence of androgens in men and estrogens in women alter numerous characteristics of immune system. However, it is depicted that sex steroid hormones despite of affecting host immunity, they also tend to affect genes and host behavior which later make men more prone to the infections [39]. Although, females tend to exhibit higher immune responses and quick clearance of infection because of higher CD4+ T cells and circulating immunoglobulins (Ig) but they more often evolve immune mediated diseases [40,41]. The risk of mortality due to all type of cancers is 1.6-fold greater in men than female [38,42].

3.3. Stress

Both acute and chronic psychological factors may lead to the dysregulation of immune responses at all the stages of life which enhance the prevalence of infections. Stress leads to the reduction in number of lymphocytes and natural killer activity consequently, suppressed the immune system. Chronic stress is promptly and constantly associated with immune dysregulation with long duration as compared to acute stress [38]. In chronically stressed population, immune testing specifies a direct relationship between immune suppression and incidence of disease [43]. Additionally, in these population there is a high declination in natural killer cells activity (10–20 %), the total number of T-cell (20 %) and also CD4: CD8 ratios which makes them more susceptible to the infections [44,45].

3.4. Alcohol consumption

Consumption of alcohol can proportionally alter a huge range of immune responses of both innate and adaptive immunity. It is well established that moderate alcohol consumption has beneficial impact on immune system by decreasing inflammation and ameliorated responses to vaccination. However, chronic or high dose of alcohol consumption may lead to the suppression of immune responses by altering B and T- lymphocytes, natural killer (NK) cells, cytokines formation. Subsequently, it may also enhance the susceptibility to various infections and diseases [46–48].

3.5. Malnutrition

Nutrition acts as an integral part which maintains normal immune responses. Micro and macro-nutrients, proteins, vitamins etc. boost the immune responses of host and provide protection against insertion of various intracellular pathogen and micro-organisms. These nutrition exhibits immunomodulatory activities by controlling on inflammation and infections. Deficiency in such type of micronutrients or proteins referred to as malnutrition, leads to the acquired immunodeficiency syndrome, consequently, augmenting the host susceptibility to development of several infections and diseases [49,50].

3.6. Environmental pollution

Environmental factors also exhibit harmful impact on host immune system. Certainly, acute exposure to air pollutants disturbs respiratory system which further may leads to the respiratory tract infections and asthma. Continual exposure of xenobiotics that is herbicides, insecticides, fungicides, pesticides and also industrial chemicals (styrenes, mercury, lead, polybrominated biphenyl) may stimulate or block the activity of various endogenous hormones, subsequently, not only affecting endocrine or reproductive system but also showing detrimental effects on immune system. Generally, these agents modulate the functions of immune system such as alteration of natural cells and lymphocytes activity, reduction in killing of tumor cells by macrophages and increase the susceptibility towards various pathogens [51,53].

4. Merits and demerits of existing synthetic immunomodulators

Numerous types of immunomodulators such as natural, synthetic and recombinant compounds are accessible to market. Pentoxifilline, levamisole, thalidomide and Isoprinosine are the most widely used synthetic compounds that exhibit potent immunomodulatory activity on biological system [54,55]. Bacille Calmette-Gu´erin (BCG) is a significant microbial immunomodulator which has been utilized for chronic time period for non-specific stimulation of immune system in chronic diseases such as cancer as well as infectious diseases [56,57]. The discovery of cytokines has led the development of various interferons and interleukins as immunotherapy in cancers [58].

In the field of immunomodulators, BCG and levamisole have been reported to show favorable therapeutic effects however, the major breakthrough was accomplished after the discovery of cyclosporine, a strong immunosuppressant which aborted graft rejection and was also utilized in autoimmune diseases [59]. Synthetic immunomodulators exhibits many beneficial effects on immune system. Despite of having numerous beneficial activities of these traditional immunomodulators, they also possess a number of unexpected adverse reactions which are also increasing with the passage of time and adversely affecting the body. The occurrence of serious adverse drug reactions restricts the continuous utilization of such compounds as well as warrants a search for new approaches that would be more effective and safer than these traditional immunomodulatory agents.

5. Phytochemicals as potent immunomodulators

Phytochemical is a collective term used for chemicals or agents obtained from plants, having distinctive structure and functions [60]. These phytochemicals performed various functions in plants for reproduction and protection including odor and color for protection and pollination, hormonal functions for growth and development, phytoalexins and allelochemicals for pathogen and herbivorous defense [61]. These are abundantly found in fruits, vegetables, whole grains, nuts, and seeds [62]. These compounds are often known as ‘secondary metabolites. Phytochemicals are classified into six main categories depending upon their chemical structure and function. These classes are carbohydrates, phenolics, lipids, alkaloids, terpenoids and other nitrogen-containing compounds (Fig. 4). Phytochemicals or secondary metabolites are commonly produced in order to response of external stimuli including infection, nutrition or alteration of climatic conditions. Additionally, these compounds are synthesized in specific parts of the plants. Till date, about 4000 phytochemicals have been identified [63, 64].

Phytochemicals also exhibit potent biological activities such as anti- oxidants, anti-inflammatory, immnomodulatory when they are administered by the humans. The potential activities exerted by these agents support the management of certain long-term diseases (cancer, cardiovascular diseases) [65,66]. In last two decades, phytochemicals have been widely researched by utilizing numerous numbers of vivo and in vitro models, which delivered the beneficial results of these compounds in ameliorating the various diseases and enhancing the quality of life.

5.1. Glycosides

Glycosides are the plant secondary metabolites containing a sugar moiety that is attached with non-sugar portions. The binding between the sugar and nonsugar moiety leads to the formation of hemiacetal. It includes the alcoholic or phenolic hydroxyl group of nonsugar and aldehyde or keto group of sugar moiety. These agents play numerous beneficial activities in animals and humans however, many plants accumulate these chemicals in inactive form which can be activated by the action of enzymes present in the body [67]. Glycosides may be categorized depending upon the glycone and aglycone moiety such as glucoside, fructoside, α-glycosides and β-

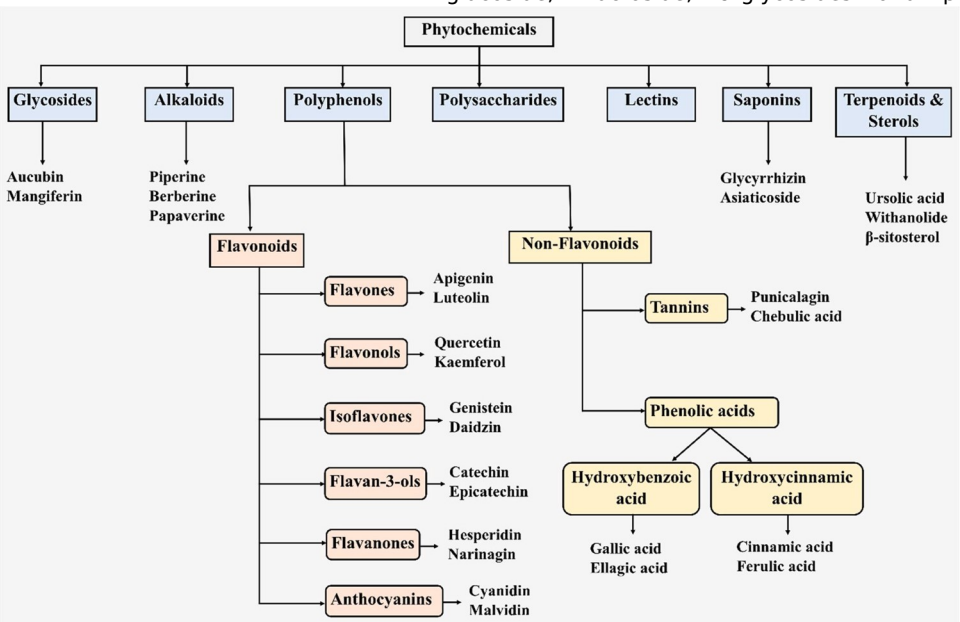


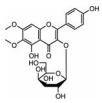
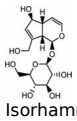
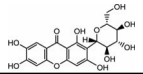
Fig. 4. Classification of Phytochemicals.

glycosides. Pharmacologically active glycosides include anthocyanin and anthracin. These compounds are mainly involved in the stimulation of central nervous system, cardiac system and immune system. Additionally, glycosides are also exhibit potent antimicrobial activity [68].

A study performed by Pandey and colleagues examined immunosuppressive activity of Eupalitin-3-*O*-β-D-galactopyranoside (Bd-I) derived from *Boerhaavia diffusa* root. Peripheral blood mononuclear cells (PBMCs) were treated with or without phytohemagglutinin (PHA) and Bd-I. Treatment of Bd-I showed a significant inhibition of TNF-α, IL- 2 and proliferation of human PBMCs [69]. Chiang and colleagues analyzed the immunomodulatory effects of Aucubin derived from *Plantago major* on PBMCs. ELISA assay was performed to analyze the expression of interferon-gamma (IF-γ). Data revealed that treatment of aucubin enhanced the proliferation of lymphocytes and formation of IL-γ. Thus, aucubin can be a potent immunostimulatory agents [70]. Zeng and colleagues performed in vivo and in vitro studies to analyze the suppressive activity of mangiferin on human epithelial ovarian cancer. ELISA, western blotting and immunohistochemistry assays were accomplished to assess the expression of matrix metalloproteinase 2 (MMP2) and matrix metalloproteinase 9 (MMP9). Data depicted a dose dependent activity of mangiferin in downregulation of expression and both MMP2 and MMP, consequently, inhibited the development of human epithelial ovarian cancer [71].

An in vitro study conducted by Akbay et al. evaluated immunomodulatory effects of isorhamnetin-3-*O*-glucoside by chemotaxis and intracellular killing activity tests. Data revealed that isorhamnetin-3-*O*- glucoside have remarkable chemotactic and intracellular killing properties [72]. Cytokines are a broad category of proteins which play a significant role in the cell signaling. Any disturbance in the production of cytokines may lead to various diseases. Guo et al. conducted a study to analyze the activity of mangiferin derived from *Mangifera indica Linn* on ovalbumin-induced asthmatic mouse model. ELISA and antibody array assay were performed to evaluate the alterations in cytokines/chemokines expression. Treatment of mangiferin decreased the expression of Th2-mediated TNF-α, IL-3, IL-4, IL-5, IL-9, IL-13, IL-17, RANTES and concurrently enhanced the expression of Th1mediated IL-2, IL-12, IL-10, IL-γ in serum. Thus, mangiferin exerts potential immunoregulatory activity by ameliorating the imbalance between the Th1/Th2 cytokines. Additionally, mangiferin suppressed the expression of GATA-3 and STAT-6 which results in anti-asthmatic property [73] (Table 1).

Table 1
Immunomodulatory Potentials of Glycosides.

Source	Compound and structure	Animal model/cell Line	Mechanism/indication	References
Boerhaavia diffusa	Eupalitin-3-*O*-β-D-galactopyranoside	PHA stimulated PBMCs	Significant inhibition of TNF-α, IL-2 and proliferation of human PBMCs	[69]
	 Aucubin		Enhanced the proliferation of lymphocytes and formation of IL-γ	
Plantago major	 Isorhamnetin-3-*O*-glucoside	PBMCs (lymphocyte transformation)	Immunostimulatory effects	[70]
Urtica dioica	Mangiferin	Neutrophils	Enhancement of intracellular killing activity and Immunomodulatory effects	[72]
Mangifera indica		Ovalbumin-induced asthmatic mouse model	Attenuation of Th1/Th2 cytokine Imbalance	[73]

5.2. Alkaloids

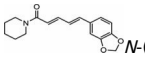
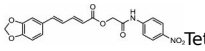
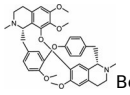
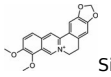
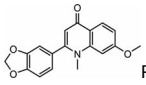
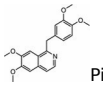
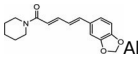
Alkaloids are the secondary metabolites which are found in numerous medicinal plants and in lower concentration in bacteria, fungi and animals. They act as defensive actions to the plants from various pathogens and insects because of their toxicity. These toxic effects are often dependent upon time of exposure, dose and various other biological factors like age, site of action as well as sensitivity. More than 10,000 molecules of alkaloids have been recognized, the first one being noscapine which was extracted from opium. They are the large single category of the secondary plant molecules which comprise one or more nitrogen atoms often in combination as a portion of cyclic structure [74, 75]. Alkaloids are a main source of performance enhancement and improving immune functions. Cocaine, nicotine, codeine, quinine, morphine and reserpine are the most demanding alkaloids, globally. They also possess considerable activity when consumed by animals. Alkaloids demonstrates

antimicrobial activity (e.g. cepharanthine), anti-tumor activity (e.g. vincristine, vinblastine) and analgesic activity (e.g. morphine). Recently, a wide variety of alkaloids have been investigated due to their anti-inflammatory and immunomodulatory activities [76,77] (Table 2).

Sunila et al. evaluated the antitumor as well as immunomodulatory activity of piperine derived from *Piper longum* on DLA and EAC induced tumor mice. Treatment of piperine at a dose of 1.14 mg for 5 days and alcoholic extract of *Piper longum* at a dose of 10 mg for 5 days significantly suppressed the development of solid tumor in mice. Additionally, administration of piperine as well as *Piper longum* increased the WBC count, bone marrow cellularity and total antibody formation [78]. Santos et al. also performed in vitro studies to investigate the immunomodulatory activities of piperine analogue by using EAC model. Treatment of N-(p-nitrophenyl) acetamide piperinoate at a dose of 6.25, 12.5 or 25 mg/kg augmented the levels of Th1 lymphocytes mediated TNF-α, IL-12, IL-1β and decreased the expressions of Th2 mediated IL-4, IL-10 as well as cell viability. Data revealed that piperine analogue has significant immunomodulatory activity [79]. Another study performed by Xue and colleagues showed the suppressive potential of tetrandrine obtained from *Stephania tetrandra* on lipopolysaccharide (LPS) induced microglial activation. Data revealed that treatment of microgalia with tetrandrine blocked the formation of NF-κB consequently, ameliorating the microglial activation [80].

Berberine is supposed to be a potent immunomodulator and serve various beneficial effects on the human body. By following this approach, a study examined the immunomodulatory activities of berberine derived from *Hydrasti Canadensis* on lung and intestine injury in endotoxemic mice. Treatment with berberine significantly suppressed the levels of NO, IFN-γ and TNF-α which were elevated by pretreatment of LPS [81]. Furthermore, sinomenine derived from *Sinomenium acutum* also exhibits immunomodulatory activity by preventing the cardiac graft rejection [82]. Manu et al. also

Table 2
Immunomodulatory Potentials of Alkaloids.

Source	Compound and structure	Animal model/cell Line	Mechanism/indication	References
Piper longum	Piperine	Dalton's lymphoma ascites (DLA) and Ehrlich ascites carcinoma (EAC) cells induced tumor mice	Increased the WBC count, bone marrow cellularity and total antibody formation	[78]
Piper nigrum	 *N*-(*p*-nitrophenyl) acetamide piperinoate	RAW 264.7 cells and mice erythrocytes EAC model	Improvement of Th1/Th2 Cytokine Imbalance Anti-tumor activity	[79]
Stephania tetrandra	 Tetrandrine	LPS-induced microglial activation	Inhibit NF-κB production and improvement in microglial activation	[80]
Hydrasti Canadensis	 Berberine	LPS-induced lung and intestine injury in mice	Suppression of NO, IFN-γ and TNF-α levels Reduction of lungs and intestine injury	[81]
Sinomenium acutum	 Sinomenine	Inbred adult male and Lewis rats (chronic cardiac allograft rejection model)	Prevention of cardiac graft rejection	[82]
Boerhaavia diffusa	Punarnavine	LPS-induced Balb/c mice	Enhanced WBC count, bone marrow cellularity and reduced the expression of proinflammatory cytokines	[30]
Opium alkaloid	 Papaverine	Mice having cerebral ischemic-reperfusion injury	Anti-inflammatory and immunomodulatory effects	[83]
Piper nigrum	 Piperine	Phytohemagglutinin-stimulated human PBMCs	Suppression in PBMCs proliferation and expression of IL-2 and INF-γ	[84]
Fumaria capreolata	 Alkaloid extract	Dextran sodium sulphate-induced colitis in mice	Reduction in microscopic and macroscopic biomarkers of intestinal inflammation Treatment of inflammatory bowel disease	[85]

evaluated immunomodulatory activity of punarnavine obtained from *Boerhaavia diffusa* on immune system by using Balb/c mice. Mice were randomly divided into two groups: control group and treated group. Data revealed that punarnavine (40 mg/kg for 5 days) treated group significantly increased the WBC count, bone marrow cellularity and reduced the levels of proinflammatory cytokines such as TNF-α, IL-1β, IL-6, induced by LPS treatment [30].

Guan et al. analyzed the potent efficacy of papaverine against cerebral ischemic-reperfusion injury by acting on various immune pathways. Treatment of papaverine modulated the activity of Th17 by reducing the expression of NF-κB, p38MAPK, RANKL and IL-23 [83]. Piperine derived from *Piper nigrum* acts as a strong immunomodulator. A study investigated the immunomodulatory activity of piperine by using human peripheral blood mononuclear cells (PBMCs). Data revealed that piperine remarkably suppressed the PBMCs proliferation and expression of IL-2 and INF-γ [84]. A recent study examined the immunomodulatory and anti-inflammatory effects of *Fumaria capreolata* L. (AFC) extract by using dextran sodium sulphate-stimulated colitis in mice. Treatment of AFC extract significantly decreased the microscopic and macroscopic biomarkers of intestinal inflammation. Additionally, AFC extract also retarded the anti-inflammatory and proinflammatory colonic expressions which signify its therapeutic activity in inflammatory bowel disease [85].

5.3. Polysaccharides

Polysaccharides are the bioactive compounds which comprise of series of monosaccharides (10 or more), which are combined together with glycosidic bonds [86]. Numerous polysaccharide and polysaccharide-proteins complexes have been extracted or isolated from plants, fungi, mushrooms, yeasts and algae, during the past three decades. Recently, plant-derived polysaccharides have gained a significant interest due to their antitumor and immunomodulatory activity [87]. The mechanism behind immunomodulatory activity of polysaccharide is their participation in innate immunity modulation, especially function of macrophage. These compounds have the ability to suppress the levels of cytokines comprising TNF-α, IL-6 and induce the cytokines including IL-2, IL-4 and IL-10. Besides, these molecules also serve as the regulation of macrophage proliferation. Several studies have proposed a relation between administrations of polysaccharides on immune system. Therefore, based upon scientific evaluation of plant-derived polysaccharide, it can be stated that such polysaccharides can be on the basis of evaluation of novel therapeutic agents which tend to exhibit immunomodulatory activity [86,88].

Gan and colleagues analyzed the immunomodulatory effects of polysaccharide-protein complex derived from *Lycium barbarum* (LB) on S180- bearing mice. After the administration of LB extract at a dose of 10 mg/kg, a significant reduction in lipid peroxidation, tumor development and enhance the macrophage phagocytosis [87]. Another study performed by Razali et al. investigate the tumor suppressive activity of SN-ppF3 polysaccharide obtained from *solanum nigrum* by modulation of immune system. Breast tumor bearing mice was treated with of SN-ppF3 at a dose of 250 mg/kg and 500 mg/kg for ten days. Data revealed a significant destruction of tumor morphology and increment of macrophages, NK cells and T-cells. Additionally, it also ameliorates the level of IL-4, TNF-α and IFN-γ [89]. Furthermore, *Aloe arborescens* polysaccharides also exhibit antitumor and immunomodulatory activity by showing significant cytotoxicity against the HepG2 human liver cancer cells. Besides, phagocytosis and lymphocytes transformation activity were also shown by these polysaccharides [90].

Polysaccharide obtained from *Helicteres angustifolia* L (HACP) also showed a potent immunomodulatory activity when it was administered by BALB/c mice having 4T1 breast tumor. The treatment of HACP at a dose of 100, 200, and 300 mg/kg for 15 days, remarkably reduced the tumor weight and expression of TNF-α, IL-1β and INF-γ. Attenuation in lung metastasis was also observed in HACP treated group. Hence, HACP plays a significant role in suppression of tumor by modulating abnormal immune system functions [91]. Recently, Li et al. also investigated the antitumor activity of astragalus polysaccharides (APS) by directly acting on the immune system. Data revealed that APS did not show direct cytotoxicity against 4T1 cells but significantly block the development of 4T1 cells by cell apoptosis and cell arrest. Moreover, APS treatment ameliorates the expression of INF-γ, IL-2 and TNF-α [92].

5.4. Lectins

Lectin often known as heterogeneous non-enzymatic group of proteins and glycoproteins which are found almost in all organisms derived from yeasts, bacteria to animal and plants. Plant-derived lectin present in corn, wheat, tomato, potato, soybean, rice, mushroom, peanut and banana and plays a significant role in the improvement of immune system functions. Numerous lectins acquire anticancer and immunomodulatory activity in vivo, in vitro and in clinical trials, hence used as the therapeutic agent [93,94]. *Viscum album* agglutinin-I (VAA-I) is a plant lectin exhibits immunomodulatory activity by altering mitochondrial transmembrane potential and increasing intracellular levels of ROS [95]. Furthermore, dietary garlic lectins derived from Allium sativum also showed a significant immunomodulatory activity when it administered to the BALB/c mice. Treatment of

garlic lectin enhanced the levels of natural antibodies in BALB/c mice [96].

Prasanna et al. conducted a study to analyze the immunomodulatory activity of onion lectin obtained from *Allium cepa* by using RAW264.7, macrophage cell line and rat peritoneal macrophages. Treatment with onlion lectin remarkably increased the formation of nitric oxide as well as stimulated the expression of cytokines including IL-12 and TNF-α at a dose of 0.1 μg/well for 24 h. Thus, it acts as an immune boosting agent by regulating Th1 immune responses [97]. Recently, a comparative study also favors the immunomodulatory activities of lectins by modulating the cascade of pro-inflammatory plus regulatory cytokines and production of nitric oxide [98].

5.5. Phenolic compounds

Polyphenols are the naturally derived secondary metabolites which are widely found in fruits, vegetables, beverages and cereals. Different fruits or herbs containing distinctive amounts of polyphenol content, for instance, berries and apples containing about 200− 300 mg polyphenols per 100 g fresh weight. Herbal beverages also contain a significant number of polyphenols [99–102]. Polyphenols comprise of an aromatic ring on which bearing one or more hydroxyl group attached to aliphatic or aromatic ring and forming a structure from simple phenolic compound to complex-high molecular weight polymers [103]. These molecules are mainly derived from shikimate, phenylpropanoid and pentose phosphate in plants. Soil composition, growing environment, cultivation technique and genetics are mainly responsible for the variation in polyphenols concentrations. Polyphenols are mainly categorized into flavonoids and non-flavonoids. Flavonoids are further subcategorized into flavones, flavanones, flavonols, Isoflavones, flavanols and anthocyanins, consisting of two aromatic rings that are attached to an oxygen heterocycle while non-flavonoids are often recognized as phenolic acids having two demonstrative subunits named cinnamic and benzoic acid [103,104]. Recently, polyphenols have gained much interest due to their biological activity as well as in food industry. Depending upon their antioxidant, antimicrobial and anti-inflammatory properties, polyphenols have demonstrated remarkable effects in numerous chronic diseases such as neurodegenerative diseases, diabetes and cardiovascular diseases [105]. Currently, a wide variety of these molecules are showing immunomodulatory activity by altering formation of nitric oxide, eicosanoids and inhibiting proinflammatory cytokines and gene expressions [106].

Kalsum et al. reported the immunomodulatory efficacy of *Propolis Trigona* extract by using prague dawley rats' model. Treatment of ethanolic extract of propolis improved the formation of nitric oxide, phagocytic index and IgG antibodies, consequently, boosting the immune responses [107]. *Plantago* species have been widely used in the cure of inflammation, infection and cancer. Chiang et al. evaluated the immunomodulatory activity of five phenolic compounds extracted from *plantago major* on human PBMCs. ELISA and BrdU immunoassay were performed to analyze the activity of phenolic chemicals on cytokine expressions. Data revealed that treatment of aucubin, ferulic acid, vanillic acid, p-coumaric acid, and chlorogenic acids significantly augmented the activity of lymphocyte proliferation and production of IFN-γ [70]. Ellagic acid derived from *Punica granatum* showed both antiapoptotic and antiproliferative activity against the HT-29 and HCT116 colon cancer cell lines when treated with a dose of 100 μg/mL [108]. Curcumin is a potent polyphenolic compound having numerous beneficial activities on health such as anti-oxidant, anti-inflammatory and anti-cancer activity. To investigate the immunomodulatory activity of diferuloylmethane (curcumin), Yadav et al. performed a study on RAW-264.7 and macrophages cells of mouse. In order to analyze the potency of diferulomethane, PHA-induced T-cell proliferation, NK cells cytotoxicity, NO production and cytokine expression were observed. Data revealed that treatment of curcumin suppress the PHA-stimulated cytotoxicity, NO production and IL-2 and T-cell proliferation [109].

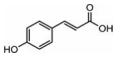
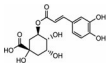
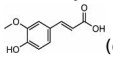
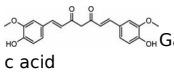
Furthermore, in vivo and in vitro studied performed by Yatoo et al., evaluated the immunomodulatory activity of *Pedicularis longiflora* and *Allium carolinianum* extract in alloxan-stimulated diabetic rats. Intervention of both the extract of *Allium carolinianum* (250 mg/kg) and *Pedicularis longiflora* (500 mg/kg) significantly decreased the levels of TGF-β1, NF-κB and TNF-α [110]. Another study also showed the antileishmania and immunomodulatory activity of gallic acid (GA) and ellagic acid (EA), natural polyphenolic compounds, against BALB/c murine macrophages. Treatment of both EA and GA, remarkably decreased the infection of macrophages induced by Leishmania major. Additionally, GA and EA enhance the phagocytosis, nitrite release and lysosomal volume consequently, improving the immune responses [111]. Recently, Park et al. examined the immunomodulatory activity of water-soluble molokhia extract (WME) obtained from *Corchorus olitorius* on cyclophosphamide-induced murine model of immunosuppression. Cytokines expression, NO production and NK cells cytotoxicity were analyzed to evaluate the activity. Data revealed that treatment of WME at a dose of 50 and 100 mg/kg remarkably augmented the leukocyte count, thymus and spleen indices and act as a potent immunostimulant [112] (Table 3).

5.6. Flavonoids

Flavonoids are significantly distributed polyphenols found plant- based foods or in beverages. More than 8000 flavonoids compounds have been identified which are mainly present in grapes, berries, cranberries, cherries and plums. These compounds are often water soluble and low molecular weight compounds containing 15 carbon atoms with C6-C3-C6 carbon skeleton. They are found in both free-state as well as in glycosides form [113]. Flavonoids are mainly categorized into two broad categories: anthocyanins (which are responsible for color in plants and fruits) and anthoxanthins (colorless molecules). Anthoxanthins are extensively classified as flavanones, flavonols, flavones, Isoflavones and flavan3-ols. Kaempferol, quercetin, myricetin, hesperetin, naringenin, epicatechingallate and anthocyanin are the main flavonoids compounds that have specific impact on human health depending upon their biological activities. Flavonoids have potential preventive activity against oxidative cell destruction and also anti-cancer activity. Besides, they have also ability to block all the processes of induction, stimulation and progression of tumor. Recently, depending upon their anti-inflammatory activity and antioxidant activity, flavonoids have been used for the control of various chronic diseases like atherosclerosis, diabetes and Alzheimer's disease [113,114]. Currently researchers are exploring their impact on immune system activity to make as the potent immunomodulators.

Chang et al. reported the immunomodulatory efficacy of centaurein flavonoid obtained from *Bidens pilosa* by regulating the expression of IFN-γ in jurkat cells. Additionally, centaurein also modulate nuclear factor of activated T-cells activity and NF-κB enhancers which depict it as a potent immunomodulator [115]. Another study analyzed the immunomodulatory potency of *Zizyphus lotus* on oxazolone-induced contact-delayed hypersensitivity (DTH) in mice at a dose of 200 mg/kg. Cytotoxicity assay was performed and revealed that methanolic extract of flavonoids notably block the DTH stimulated by oxazolone [116]. Furthermore, Abd-Alla and colleagues conducted a study to explore the immunomodulatory effects of flavonoids compounds extracted from *Jatropha curcas* on one-day-old specific pathogen-free (SPF) chicks. A considerable stimulation in both humoral as well as cell-mediated immune response were noticed after treatment with methanolic extract containing Apigenin 7-*o*-β-D-neohesperidoside, orientin, vitexin and apigenin 7-*O*-β-D-galactoside flavonoids [117]. Silymarin is a complex of flavonolignans which are obtained from *Silybum marianum* have been widely used for the antioxidant and anti-inflammatory activity. Depending upon its beneficial effects on human body, Gharagozloo et al. investigated the immunomodulatory activity of silymarin by using CD4+ splenocytes from C57/Bl6 mice. ELISA and proliferation assay were performed to

Table 3
Immunomodulatory Potentials of Phenolic Acids.

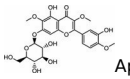
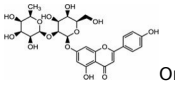
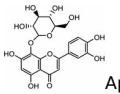
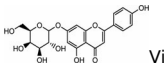
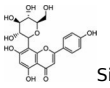
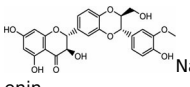
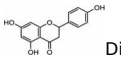
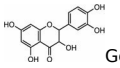
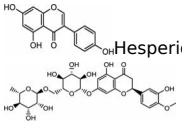
Source	Compound and structure	Animal model/cell Line	Mechanism/indication	References
Plantago major	p-coumaric acid	PBMCs (lymphocyte transformation)	Augmented IFN-γ production and proliferation of lymphocyte	[70]
Plantago major	Vanillic acid 	PBMCs (lymphocyte transformation)	Augmented IFN-γ production and proliferation of lymphocyte	[70]
Plantago major	Chlorogenic acids	PBMCs (lymphocyte transformation)	Augmented IFN-γ production and proliferation of lymphocyte	[70]
Plantago major	Ferulic acid 	PBMCs (lymphocyte transformation)	Augmented IFN-γ production and proliferation of lymphocyte	[70]
Curcuma longa	Diferuloylmethane  (curcumin)	PHA stimulated T-cell proliferation, NK cell cytotoxicity, production of cytokines by human PBMCs, NO production in mouse macrophage cells, RAW-264.7	Augmented NK cell cytotoxicity and inhibits IL-2, NF-κB and NO production	[109]
Anacardium occidentale, Myracrodruon urundeuva, Anogeissus leiocarpus	 Gallic acid	Cytotoxic BALB/c murine macrophages	Enhance the phagocytosis, nitrite release and Improve immune responses Reduction of infection and infectivity of macrophages	[111]
Anacardium occidentale, Myracrodruon urundeuva, Anogeissus leiocarpus	Ellagic acid	Cytotoxic BALB/c murine macrophages	Enhance the phagocytosis, nitrite release and Improve immune responses Reduction of infection and infectivity of macrophages	[111]

analyze the suppressive activity on cytokine expressions. Data revealed that treatment of silymarin remarkably inhibit CD4+ cells proliferation and formation of INF-γ and IL-2. Further, silymarin inhibited the p65/NF-B phosphorylation in CD4+ T cell which suggest that silymarin may be used as a potent immunosuppressive agent [118].

Citrus fruits also exhibited potent antioxidant, anti-inflammatory and immunomodulatory activity for the management of fibrosis, acute hepatis, sepsis and cancer. Yilma et al. reported the immunomodulatory effects of naringenin derived from citrus fruits using J774 macrophages of mouse. Treatment of naringenin downregulated the expression of chemokines (CXCL1, CCL4, CCL5, CXCL5, CXCL10) and cytokines (IL-6, IL-10, IL-1β, IL-12p70, TNF, IL-1α) in a dose dependent pattern [119, 120]. Furthermore, a study analyzed the immunomodulatory activity of dihydroquercetin flavonoid (*Cedrus deodara*) on immune status of gilthead seabream. Fish were divided into four groups: control group (no dihydroquercetin), 0.1 % dihydroquercetin administration, 0.5 % dihydroquercetin administration and 1.0 % dihydroquercetin administration. Data revealed that treatment with lower dose significantly showed maximum results in enhancing the immune status and IgM levels of gilthead seabream [121]. Recently, genistein and hesperidin flavonoids showed immunomodulatory effects against LPS-challenged broilers. Chicks were randomly divided into different groups and treated with genistein and hesperidin alone as well as combination of both. The results revealed that treatment of both flavonoids improved

Table 4

Flavonoids as Immunomodulators.

Source	Compound and structure	Animal model/cell Line	Mechanism/indication	Referenc es
Bidens pilosa	Centaurein	Human leukemic T cells and Jurkat cells	Immunomodulatory effects by regulating IFN-γ expression	[115]
Jatropha curcas	 Apigenin 7-*o*-β-D- neohesperidoside	One-day-old SPF chicks	Stimulation humoral and cell-mediated immune responses Protection against Newcastle disease	[117]
Jatropha curcas	 Orientin	One-day-old SPF chicks	Stimulation humoral and cell-mediated immune responses Protection against Newcastle disease	[117]
Jatropha curcas	 Apigenin 7-*O*-β-D-galactoside	One-day-old SPF chicks	Stimulation humoral and cell-mediated immune responses Protection against Newcastle disease	[117]
Jatropha curcas	 Vitexin	One-day-old SPF chicks	Stimulation humoral and cell-mediated immune responses Protection against Newcastle disease	[117]
Silybum marianum	 Silymarin	CD4+ splenocytes from C57/Bl6 mice	Inhibit CD4+ cells proliferation, formation of INF-γ and IL-2 and p65/ NF-B phosphorylation	[118]
Citrus fruit	 Naring enin	J774 macrophages of mouse infected with *Chlamydia trachomatis*	Downregulated the expression of chemokines and cytokines	[119,120]
Cedrus deodara	 Dihydroquercet in	Gilthead seabream	Enhancement in immune status and IgM levels Immunostimulant activity for resist and/or treat disease problems	[121]
Flavonoid	 Genistein	LPS-stimulated broilers	Improvement of humoral and mucosal immunity Anti-Newcastle disease Anti-avian influenza antibody	[122]
Flavonoid	 Hesperidin	LPS-stimulated broilers	Improvement of humoral and mucosal immunity Anti-Newcastle disease Anti-avian influenza antibody	[122]

the humoral as well as mucosal immunity by enhancing the intestinal intraepithelial lymphocyte counts [122] (Table 4).

5.7. Anthocyanins

Anthocyanins, a class of polyphenols, are the water-soluble pigments and can have color modification from red to yellow in many fruits and vegetables. These pigments of anthocyanins are known as anthocyanidin glycosides. These are promptly present in outer layer of numerous fruits such as cranberries, raspberries, red grapes, black currants, blueberries, bilberries and strawberries. Cyanidin, malvidin, peonidin, pelargonidin and delphinidin are the most widely investigated

anthocyanins. These compounds have shown promising antioxidants and anti-inflammatory activity by modulating various signaling pathways. These favorable effects tend to investigate the immunomodulatory activity of anthocyanin [114,123].

A study investigated the immunomodulatory and antioxidant

efficacy of anthocyanins derived from cherries on adjuvant-induced arthritis (AIA) in rats by analyzing the expressions of IL-6, prostaglandins E2 (PGE2) and TNF-α. Study including the administration of anthocyanins extract containing cyanidin, delphinidin, petunidin, malvidin and peonidin with a dose of 75, 150, 300 mg/kg, daily for 28 days. Data revealed that anthocyanins content remarkably suppressed the paw swelling, cytokines expressions including IL-6, TNF-α and PGE2 [124]. An ex vivo in human study performed by Rechner and Kroner reported the anti-inflammatory activity of cyanidin-3-glycoside, peonidin by improving the platelets function [125]. Furthermore, Xu et al. conducted a comparative study to evaluate the immunomodulatory activity of anthocyanins fraction on LPS-induced human monocytes mono mac 6. Data revealed that there is no significance difference between the immunomodulatory and antioxidant activity of both anthocyanins fraction and resveratrol [126]. Recently, numerous other studies also reported the antioxidant and immunomodulatory activity of anthocyanins including cyanidins, delphinidin, peonidins and malvidins by decreasing levels of IL-6, TNF-α and improving the insulin sensitivity [127–129] (Table 5).

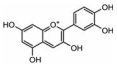
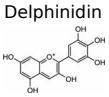
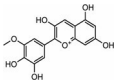
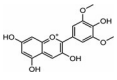
5.8. Tannins

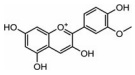
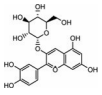
Tannins are large molecular weight, water soluble compounds, often present in plants as a complex with proteins, polysaccharides and alkaloids. Depending upon their solubility or hydrolysis product, tannins are divided into hydrolysable tannins, proanthocyanidins, phlorotannins. Hydrolysable tannins are formed from the esters of gallic acid, condensed tannins are combined structure of polyhydroxy flavan-3-ol monomers and phlorotannins are formed from phloroglucinol, extracted from brown algae. Apple, grape, berries, peach walnuts are the major sources of tannins [130,131]. Many preclinical studies have shown the immunomodulatory activity of these compounds.

Punicalagin (PCG) is an ellagitannin, which exhibits various beneficial effects on human body. Lee et al. investigated the immunosuppressive activity of PCG derived from *Punica granatum* depending upon its action on nuclear factor of activated T cells (NFAT). Data revealed that treatment of PCG suppressed the expression of IL-2, leukocyte reaction as well as CD3 + T cell infiltration. Additionally, PCG also showed some free radical scavenging activity which suggests that PCG could be a potent immunosuppressant [132]. Another study conducted by Reddy Reddanna reported the immunosuppressive activity of Chebulagic acid (CA) derived from *Terminalia chebula* on LPS-induced RAW 264.7 cell line. Treatment of CA significantly attenuated the expression of IL-2, TNFα and ROS production. In addition, a dose dependent pattern was also seen in inhibition of NF-κB activation, p38, JNK and ERK ½ phosphorylation [133]. Furthermore, methanolic extract of *Pongamia glabra* (PGE) exhibited the immunomodulatory activity in cyclophosphamide induced myelosuppressed mice when it was treated with a dose of 250 and 500 mg/kg, daily for 13 days. On 14th day, data revealed that PGE improve the WBC, platelets and DLC counts in a dose dependent manner [134]. Furthermore, Corilagin extracted from *Terminalia chebula* showed the neuroprotective activity by downregulating the H2O2 stimulated PC12 cells death [135].

A recent study performed by Ilangkovan et al. evaluated the immunomodulatory activity of *Phyllanthus amarus* extract (corilagin, hypophyllanthin, geraniin, phyllanthin) by using Balb/C Mice. Experimental protocol involved treatment of mice with extract at a dose of 50, 100 and 200 mg/kg, daily for 14 days. A dose dependent pattern was followed to

Table 5
Immunomodulatory Activity of Anthocyanins.

Source	Compound and structure	Animal model/ cell Line	Mechanism/ indication	References
Prunus cerasus ledeb	Cyanidin 	AIA rats	Suppression of paw swelling and cytokines expression	[124,127, 128,129]
Prunus cerasus ledeb	Delphinidin 	AIA rats	Suppression of paw swelling and cytokines expression	[124,127, 128,129]
Prunus cerasus ledeb	Petunidin 	AIA rats	Suppression of paw swelling and cytokines expression	[124]
Prunus cerasus ledeb	Malvidin 	AIA rats	Suppression of paw swelling and cytokines expression	[124]

Prunus cerasus ledeb, Blackberry	Peonidin 	AIA rats	Suppression of paw swelling and cytokines expression	
		Ex-vivo human platelets	Anti-inflammatory activity	[124,125, 127,128, 129]
Blackberry	cyanidin-3-glycoside 	Ex-vivo human platelets	Anti-inflammatory activity Improve platelets function	[125]

inhibit the production of NO and myeloperoxidase activity. Additionally, it also improved both cellular and humoral immune responses in treated mice [136].

5.9. Saponins

Saponins are the class of naturally occurring glycosides which are widely present in different parts including leaves, flowers, shoots, roots, tubers and seeds [137]. These are complex compounds having non-sugar (aglycone) part which is attached with sugar moiety. Depending upon their aglycone skeleton, saponins can be divided into two categories. The first class consists of triterpens saponins, which are mainly present in dicotyledonous angiosperms. The second class contains steroidal saponins which are mainly present in monotyledonous angiosperms. Glycone part of saponins are mostly oligosaccharides occurs in linear or branched chain bound with the hydroxyl group by acetal linkage. Many researchers have demonstrated the potential of plant derived saponins to induce immunogenicity of various vaccine, in in vivo and in vitro studies. The use of saponins as the immunoadjuvants, for their modulating cell-induced immune system and promoting the production of antibodies, is one of the most prominent activities of saponins [137, 138]. Various saponins compounds have ability to inhibit the cancer cells by arresting cell cycle and apoptosis. Ablise et al. evaluated the immunotherapeutic activity of Glycyrrhizin derived from *Glycyrrhiza glabra* on rat liver microsomes. Treatment of glycyrrhizin with 1.0 mg/mL significantly inhibit the classical complement pathway and enhanced the antioxidant activity [139]. Another study performed by Punturee et al. reported favorable effects of Asiaticoside saponin extracted from *Centella asiatica* by using PBMCs. Data revealed that treatment of asiaticoside with 100 mg/kg significantly phagocytic index and total WBC count when compared to not treated group. Additionally, it also improve the cellular and humoral immune responses [140].

Furthermore, Nalbantsoy and colleagues evaluated the immunomodulatory and anti-inflammatory activity of cycloartane type saponins from *Astragalus oleifolius* for the treatment of leukemia and wound healing by using male swiss albino mice. ELISA assay was performed to analyze the effects on cytokines expression and immune responses. The results showed that treatment of Macrophyllosaponin B and Astragaloside VII solution at a dose of 156 μg/mL improve the Th1-mediated cytokines (IFN-γ, IL-2) and downregulated the Th2-mediated cytokines (IL-4) expressions. Thus, both novel compounds can be used as the potent immunoregualtors [141]. Another study reported the immunomodulatory activity of *Calendula officinalis* extract by using BALB/c mice. Treatment of extract containing oleanolic acid 3-*O*-glucuronides at a dose of 100 μg × mL^{-1} modulate the cytokines formation in mice [142]. Sun et al. showed the immunomodulatory activity of *Albizia julibrissin* saponins (AJS) against 0.5 % rabbit red blood cell suspension. Data revealed that the treatment of AJS at a dose of 2.53 μg/mL significantly improved the cellular and humoral immune response as well as Th1/Th2 cytokines production [143].

A study reported the immunostimulatory activity of ginseng when it was treated at a dose of 2.5, 5 and 10 mg/kg in chickens, by improving the vaccination in immunosuppressed chickens [144]. Furthermore, the similar results were showed by the *Quillaja brasiliensis* when prepared with experimental vaccines against bovine herpesvirus type 1 and 5, bovine viral diarrhea virus and poliovirus in mice model. The treatment of adjuvant improves the improved the immune responses and protect lethal challenge in mice [145]. Another study performed by Wu and colleagues evaluated the beneficial activity of Ilexsaponin I derived from *Ilex pubescen* in LPS-induced RAW 264.7 cells. Data revealed that treatment of Ilexsaponin I at a dose of 30 or 10 mM restricted the formation of PGE2 and NO by downregulated the expression of cyclooxygenase-2 and iNOS [147]. Davidianoside F saponin also exhibits the anti-inflammatory activity in human tumor cell lines by suppressing the IL-1β [147].

Recently, Aslanipour et al. evaluated that immunomodulatory effects of saponins derived from *Astragalus karjaginii* and *Astragalus brachycalyx* on human whole blood. The results depicted that extract of both plants improve the induction of cytokines production and immune responses [148,149] (Table 6).

5.10. Terpenoids

Terpenoids, secondary metabolites, are the naturally occurring compounds often known is isoprenoids because of containing isoprene units. These compounds are derived by mevalonate (MVA) and 2-*C*- methyl-D-erythriol 4-phosphate (MEP) pathways. MVA pathway is mainly leads to formation of hemi, mono, di and triterpenoids whereas MEP pathway leads to the formation of tri and sesquiterpenoids [150, 151]. Terpenoids is a large class of phytochemicals, often present in higher plants. Mostly terpenoids are found in plants however, some are present in yeasts and bacteria. Their structure contains six isoprene units which are biosynthetically derived from the C_{30} hydrocarbon, squalene. Carvone, retinol, perillyl alcohol, betulinic acid, β-carotene and α-carotene are the most common examples of terpenoids. In plants, triterpenoids possess the defensive and microbial protective activities. These compounds also exhibit numerous therapeutic activities such as antiviral, anti-diabetic, anti-inflammatory antispasmodic and immunomodulatory activities. The favorable effects of terpenoids on immune system are mainly occurred either production of antibodies or improving T-cell response suppression [151,152].

Chiou and colleagues evaluated the immunomodulatory activity of andrographolide extracted from *Andrographis paniculata* by using RAW 264.7 cells. A dose dependent activity of andrographolide (1 ± 100 mM) in suppressing the production NO and iNOS was observed [153]. Another study reported the cytokines modulating activity of boswellic acid derived from *Boswellia serrate* in paw edema rat and AIA models. Data revealed that the treatment of boswellic acid at a dose of 0.25 mg/paw, downregulated the activity of pro-inflammatory mediators and also showed anti-arthritic activity [154]. Podder et al. reported the immunosuppressive effects of ursolic acid (UA) in macrophage THP-1 cell line. Treatment of UA significantly lowered the intracellular Mycobacterium count by generating NO and ROS. In addition, it also activates the phagocytosis process in human monocyte cells and THP-1 cells which suggests the intracellular killing effects of UA in *Mycobacterium tuberculosis* infection [155].

Recently, Banerjee et al. evaluated the immunomodulatory activity of Spergulin-A estrated from *Glinus oppositifolius* for the management of visceral leishmaniasis (VL). Treatment of spergulin-A with a dose of 30 μg/mL, showed a significant activity against intracellular parasites. The enhancement in pro and anti-inflammatory activity favor the use of spergulin-A in VL [156] (Table 7).

5.11. Sterols and sterolins

The introduction of glucocorticoids into our armory of drugs revolutionized the approach for the management of chronic inflammatory and immune system related diseases. Sterols and sterolins are mainly present in plants but not in animals thus, we obtain from diet. Numerous in vitro ex vivo studies have reported their immunomodulatory activity by altering the cellular proliferation of T-cells and enhancing the activity of NK-cells in some types of cancer. It has also been proposed that the sterols and sterolins have ability to regulate the levels of Th1 and Th2 mediated cytokines which further helps in the improvement of immune responses. Even very low concentrations of phytosterols, β-Sitosterol, and its glycoside have ability to improve the proliferative responses of T- cells which make them potent immunomodulators [162,163].

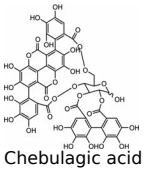
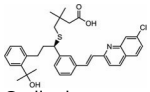
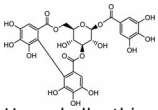
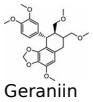
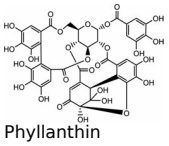
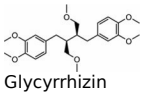
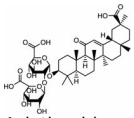
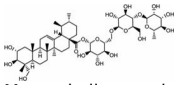
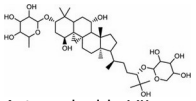
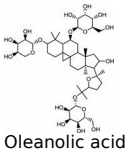
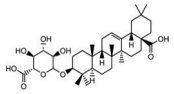
Rasool et al. investigated the immuomodulatory activity of Withanolide extracted from W*ithania somnifera* by using albino Wistar strain rats. Administration of withanolide to the rats significantly suppressed the classical complement pathway, hypersensitivity reactions and mitogen stimulated lymphocyte proliferation. Thus, the study favors the development of withanolide as a potent immunosuppressive agent [157]. Furthermore, β-sitosterol and daucosterol also showed the imunomodulatory activity by improving the Th1 and Th2 immune responses against disseminated candidiasis in mice [158]. Another study performed by the Lee and colleagues reported the immunomoulatory activities of phyosterols extracted from *Clinacanthus nutans* by using murine cells. Mitogen induced B and T-cells proliferation, release of helper T-cell cytokines were examined to analyze the immunosuppressive of phytosterols (stigmasterol, shaftoside, β-sitosterol). Data revealed that treatment of phytosterols significantly decreased the T-cell proliferation and improved the Th1 and Th2 mediated cytokines expression [160].

Boubaker et al. reported the immunomodulatory effects of β-sitosterol isolated from *Nitraria retusa* in BALB/c Mice. MTT assay was performed to analyze the macrophages and lumphocytes proliferative activity of β-sitosterol. Treatment of β-sitosterol remarkably inhibited the tumor progression, enhanced the splenocytes proliferation, protected the lung parenchyma and also blocked the lipid peroxidation. All these effects of β-sitosterol are due to improvement of immune responses [161]. Moreover, β-sitosterol and daucosterol isolated from *Dioscorea batatas* reported the immunmodulatory effects on LPS-induced RAW 264.7 and TK-1 Cell line. Treatment of both β-sitosterol showed the immune boosting effects in RAW 264.7 cells by enhancing the expressions of iNOS and TNF-α while it showed immunosuppressive activity in TK-1 cells by lowering the expression of TNF-α. Daucosterol showed the immunosuppressive effects in both RAW 264.7 and TK-1 Cell line by inhibiting the expressions of IL-6, iNOS and TNF-α [159].

6. Future directions

There is a vast area of research which mainly focuses on phytochemicals as they serve as alternative therapeutics for the management of numerous chronic diseases viz. rheumatoid arthritis, diabetes, asthma and cardiovascular diseases. Phytochemicals have been proved to be cost effective as well as easily extracted from the plants. Despite of fact that in vitro and in vivo studies have depicted phytochemicals as potent

Table 6
Immunomodulatory Activity of Tannins and Saponins.

Source	Compound and structure	Animal model/cell Line	Mechanism/indication	References
Punica granatum	Punicalagin	PMA-induced chronic ear edema model in Balb/c mice	Immunosupressive action	[132]
				
Terminalia chebula	Chebulagic acid	LPS-stimulated RAW 264.7 cell line	Downregulation of IL-2, TNF-α and ROS production	[133]
				
Terminalia chebula	Corilagin	H2O2-induced toxicity and neurodegenerative disease in PC12 cells	Neuroprotection	[135]
				
Phyllanthus amarus	Hypophyllanthin	Sheep red blood cells-induced swelling rate of Balb/C mice paw	Immunomodulatory activity	[136]
				
Phyllanthus amarus	Geraniin	Sheep red blood cells-induced swelling rate of Balb/C mice paw	Immunomodulatory activity	[136]
				
Phyllanthus amarus	Phyllanthin	Sheep red blood cells-induced swelling rate of Balb/C mice paw	Immunomodulatory activity	[136]
				
Glycyrrhiza glabra	Glycyrrhizin	Cytochrome P450/NADPH reductase system from rat liver microsomes	Inhibition of Classical complement pathway	[139]
				
Centella asiatica	Asiaticoside	Human PBMCs	Enhancement of total WBC count and phagocytic index	[140]
				
Astragalus oleifolius	Macrophyllosaponin B	LPS-induced male swiss albino mice (six to eight weeks old)	Attenuation of Th1/Th2 Cytokine Imbalance	[141]
				
Astragalus oleifolius	Astragaloside VII	LPS-induced male swiss albino mice	Attenuation of Th1/Th2 Cytokine Imbalance	[141]
				
Calendula officinalis	Oleanolic acid 3-*O*-glucuronides	BALB/c mice infected with larvae	Immunomodulatory activity Improve cytokine production	[142]
				

(*continued on next page*)

Table 6 (*continued*)

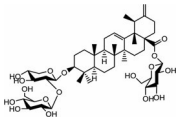
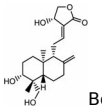
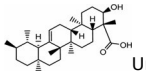
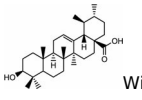
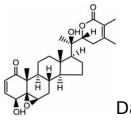
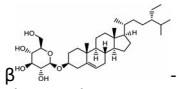
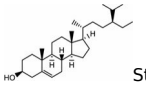
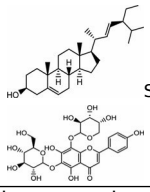
Source	Compound and structure	Animal model/cell Line	Mechanism/indication	References
Ilex pubescen	 Ilexsaponin I	LPS-stimulated NO, PGE2 production in RAW 264.7 macrophages	Inhibited PGE2 production and NO production	[146]

Table 7
Terpenoids and Sterols as Immunomodulators.

Source	Compound and structure	Animal model/cell Line	Mechanism/indication	References
Andrographis paniculata	Andrographolide	NO produced RAW 264.7 cells	Suppression of NO and iNOS production	[153]
Boswellia serrate	 Boswellic acid	Rat paw edema modeling	Downregulation of pro-inflammatory mediators and anti-arthritic activity	[154]
Terpenoids (apples, cranberries, oregano, rosmary, peppermint)	 Ursolic acid	Macrophage THP-1 cell line	Stimulates intracellular killing activity of macrophages during Mycobacterium tuberculosis infection	[155]
Withania somnifera	 Withanolide	Arthritis induced albino wistar strain rats	Suppression of classical complement pathway and hypersensitivity	[157]
Astragalus membranaceus	 Daucosterol	LPS-stimulated RAW 264.7 and TK-1 Cells of BALB/c female mice	Improvement of Th1 and Th2 immune responses	[159,160]
Clinacanthus nutans	 β-sitosterol	C57BL/6 male mice Tumor induced BALB/c mice	Attenuation of T-cell proliferation and improvement of Th1 and Th2 imbalance Antitumor activity	[159,160, 161]
Clinacanthus nutans	 Stigmasterol	LPS-stimulated C57BL/6 male mice	Attenuation of T-cell proliferation and improvement of Th1 and Th2 imbalance	[160]
Clinacanthus nutans	 Shaftoside	LPS-stimulated C57BL/6 male mice	Attenuation of T-cell proliferation and improvement of Th1 and Th2 imbalance	[160]

medications against cell cultures and animal models with accentuating the mechanism of action, still there is a lack of research with respect to clinical studies. In order to examine the effects of phytochemicals on immune system, liver and upon other vital tissues, it is significant to evolve the area of research from laboratory testing to clinical studies. The data obtained from the clinical trial can also be utilized to determine the potential risks associated with phytochemicals. For any therapeutic agent, success can be determined on the basis of cellular target at molecular level. Consequently, till date, there is a lack of standardization to active ingredient, qualitative and quantitative modification in preparations as well as lack of clinical studies are the major factors which are responsible for the inconsistency in the immunomodulatory effects of phytochemicals in previous experiments.

Such inconclusive results have indicated the incomplete descriptive knowledge regarding mode of action of phytochemicals which raises many questions on safety and efficacy of phytochemicals. One of the major challenges include standardization of dosages of phytochemicals which has not probably been overcome yet. Numerous research institutions as well as global companies including Chromadex, Horizon Science, and American institute for cancer research are working on various projects in order to depict the safety and efficacy of various phytochemicals which can be able to treat many chronic disorders.

7. Conclusion

The presence of active ingredients in medicinal plants has always showed an essential source of clinical therapeutics due to their multi- pharmacological activities. The use of medicinal plants in traditional medicines for the health benefits is well studied. Any imbalance between the immune system leads to the development of numerous life-threatening ailments such as diabetes, rheumatoid arthritis and cancer. In some recent studies, the treatment of such diseases can be possible by phytochemicals which are found in specific plants species. In vivo, in vitro and ex vivo studies have reported that the administration of phytochemicals such as quercetin, ellagic acid, mangiferin and withanolide, significantly reduced the occurrence of immune-related diseases due to their antioxidant, anti-inflammatory and immunomodulatory activities. Moreover, phytochemicals tend to improve the Th1 and Th2 mediated cytokines expressions which result in suppression of autoimmune diseases. Despite of having several preclinical and ex vivo studies, convenient evidences are required to confirm the immunomodulatory activity of phytochemicals in the prophylaxis and cure of immune-related diseases. Certain improvements in parameters such as standardize dosage and interventional period are still required to develop phytochemicals as the ideal immunomodulators.

Declaration of Competing Interest

The authors report no declarations of interest.

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